

REMARKS

I. Status of the Claims

Claims 23-42 are pending in this application. Claims 39-42 stand withdrawn from further consideration under 37 C.F.R. § 1.142(b). Claims 23-33 stand rejected under 35 U.S.C. § 103(a). Claims 34-38 stand rejected under 35 U.S.C. § 112, second paragraph. Claim 34 has been amended. Support for the amendment may be found in the as-filed specification. No new matter has been added by this amendment.

II. The Claims Are Not Obvious

The Examiner has maintained the rejection of claims 23-33 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Zanta *et al.* in view of Neidigh *et al.* for the reasons of record set forth in the Office Action mailed January 14, 2003 ("the previous Office Action"). Applicants respectfully traverse for the reasons of record, and for the following additional reasons.

In the previous Office Action, the Examiner asserted that it would have been obvious to one of ordinary skill in the art at the time this application was filed to modify the method for functionalization of polyethyleneimine as allegedly taught by Zanta *et al.* with the conditions for reductive amination allegedly taught by Neidigh *et al.* Office Action mailed January 14, 2003, at pages 5-6.

In response, Applicants argued that the cited references alone, or in combination, fail to teach or suggest all the elements of claims 23-33. Amendment filed March 24, 2003, at page 7. These claims recite a process for making functionalized polyalkyleneimines, wherein a polyalkyleneimine is treated with a functionalized hemiacetal in the presence of titanium (IV) isopropoxide and sodium borohydride in an

alcoholic solvent. *Id.* In contrast, Neidigh *et al.* only disclose a method for making N-methyl secondary amines by reacting an aldehyde or a ketone with a primary amine, triethylamine, and titanium (IV) isopropoxide in the presence of ethanol (followed by treatment of the mixture with sodium borohydride). *Id.* The claimed process is clearly distinguishable from Neidigh *et al.* in that Applicants do not use an aldehyde or ketone as the starting material. In addition, triethylamine is not used in the claimed process. *Id.*

Applicants also argued that there is no teaching or suggestion in the references that the method of Neidigh *et al.* is useful for coupling hemiacetals, especially functionalized hemiacetals with other reactive groups, to polyalkyleneimines. *Id.* Moreover, Applicants noted that the Examiner had not provided any evidence that one skilled in the art would have a reasonable expectation of success in (1) leaving out triethylamine or (2) using Neidigh's disclosed reaction conditions to couple a functionalized hemiacetal to a polyalkyleneimine. *Id.*

In response to Applicants' earlier arguments, the Examiner now asserts that one of ordinary skill in the art would have had a reasonable expectation of success in using the Neidigh *et al.* reaction conditions to couple a functionalized hemiacetal to a polyalkyleneimine since this reaction comprises a reductive amination reaction, and the process of Neidigh *et al.* clearly provides a means for reductive amination of aldehyde or ketone compounds. Office Action mailed June 3, 2003, at page 2. The Examiner also asserts that Neidigh *et al.* teaches that the method is general for a variety of aldehydes and ketones. *Id.* Moreover, in regard to leaving out the triethylamine, the Examiner contends that the instant claims are drawn to a process comprising treating a

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polyalkyleneimine with a functionalized hemiacetal in the presence of titanium (IV) isopropoxide and sodium borohydride. *Id.* at pages 2-3. According to the Examiner, the breadth of the instantly claimed process encompasses the use of triethylamine and, therefore, it is not necessary that the process of Neidigh *et al.* leave out triethylamine in order to render obvious the claimed process. *Id.* at page 3.

The Examiner further contends that Zanta *et al.* provides a method for functionalization of polyethyleneimine by means of glycosylation, wherein the glycosylation method comprises reductive amination, and wherein the method comprises the use of sodium borate. *Id.* According to the Examiner, one of ordinary skill in the art would recognize that the glucose subunit used in Scheme I of Neidigh *et al.* is a cyclic hemiacetal. Citing M.P.E.P. § 2144.05, the Examiner concludes that absent evidence to the contrary, "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *Id.* The Examiner alleges that, in the instant case, Zanta *et al.* provides the general conditions necessary for reductive amination of a polyethyleneimine with a hemiacetal-containing compound.

For the reasons of record, Applicants maintain their assertion that the cited references fail to teach or suggest all the claim elements when taken alone or together (e.g., use of Neidigh's method with polyalkyleneimine as starting material). Moreover, the cited references fail to provide a reasonable expectation of success (e.g., use of Neidigh's method to prepare molecules capable of mediating gene delivery to cells).

Without acquiescing in the arguments set forth by the Examiner, Applicants respectfully assert that the Examiner has failed to fully and adequately address

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Applicants' prior traversal. To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. See M.P.E.P. § 2143.01. The mere fact that references can be combined or modified does not render the resulting combination obvious unless the prior art also suggests the desirability of the combination. *Id.*

The Federal Circuit does not take the requirement for motivation lightly, stating that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is *rigorous* application of the requirement for a showing of . . . motivation. . . . The showing must be *clear and particular*." See *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999) (emphasis added).

In more recent cases, the Federal Circuit has held that determinations of *prima facie* obviousness must be supported by a finding of "substantial evidence." See *In re Zurko*, 258 F.3d 1379, 1386 (Fed. Cir. 2001). Specifically, unless "substantial evidence" *found in the record* supports the factual determination central to the issue of patentability, the rejection is improper and should be withdrawn. See *Zurko*, 258 F.3d at 1386.

On January 18, 2002, the Federal Circuit again affirmed the Office's high burden to establish a *prima facie* case of obviousness. Specifically, the Federal Circuit held that "[t]he factual inquiry whether to combine references must be *thorough and searching*. It must be based on objective evidence of record. The precedent has been reinforced in myriad decisions, and cannot be dispensed with." *In re Sang-Su Lee*, 277

F.3d 1338, 1343 (Fed. Cir. 2002) (emphasis added; internal quotations and citations omitted).

In arguments presented in the Office Action mailed January 14, 2003, and maintained in the present Final Office Action, the Examiner asserts that “[o]ne of ordinary skill in the art at the time of filing would have been motivated to make this modification since the use of the sodium cyanoborohydride reagent in the method of Zanta *et al.* is compromised by its cost and toxicity, specifically the risk of residual cyanide in the product.” Office Action mailed January 14, 2003, at page 6. However, there is no indication in Zanta *et al.* that the use of cyanoborohydride in the glycosylation of polyethyleneimine causes subsequent impairment of gene delivery to cells. Moreover, there is no suggestion that the transfection efficiency of polyethyleneimine can be improved by an alternative method of functionalization. Lastly, there is no teaching or suggestion that the compounds prepared by the method of Neidigh *et al.* may be used for gene delivery to cells. Therefore, looking at the references as a whole, there would not have been the “clear and particular” motivation to use the method of Neidigh *et al.* to modify the method of Zanta *et al.*, which is necessary to establish a *prima facie* case of obviousness. Nor has the Examiner provided the requisite “thorough and searching” analysis required to determine whether the teachings of the two references should be combined.

In summary, Applicants maintain and extend their previous assertion that the cited prior art references (1) fail to teach or suggest all the claim elements when taken alone or together, (2) fail to provide a reasonable expectation of success, and (3) fail to

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provide motivation to modify or combine teachings. Therefore, Applicants respectfully submit that the Examiner has failed to make a *prima facie* case of obviousness.

For the reasons above, Applicants respectfully request the reconsideration and withdrawal of the rejection of claims 23-33 under 35 U.S.C. § 103(a).

III. The Claims Are Definite

The Examiner rejected claims 34-38 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Office Action at page 4. According to the Examiner, there is insufficient antecedent basis for the phrase "the reaction" in claim 34. *Id.*

Applicants respectfully submit that claim 23 clearly informs the skilled artisan that "the reaction" carried out is the coupling of a functionalized hemiacetal to a polyalkyleneimine as claimed in claim 23 (i.e., the reaction between a polyalkyleneimine and a functionalized hemiacetal in the presence of titanium (IV) isopropoxide and sodium borohydride). Solely to expedite prosecution and without acquiescing in the rejection, Applicants have amended claim 34 to recite "the process according to claim 23."

The Examiner also asserts that "the metes and bounds of [the phrase "targeting element"] is vague and indefinite since [claim 34] does not indicate what the compound is targeting, and it does not define the structure of this element." *Id.* According to the Examiner, "[o]ne of ordinary skill in the art would not be reasonably apprised of the scope of the claimed invention, since neither the specification as filed nor the claims

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provides an adequate definition of the term "targeting element" as used in this context."

Id.

Applicants respectfully maintain that the specification clearly informs the skilled artisan that targeting elements are moieties that direct (i.e., target) the transfer of functionalized polyalkyleneimine-nucleic acid complexes toward desired cell types, certain desired tissues, or certain desired cell compartments. See Amendment filed March 24, 2003, at pages 4-5 and Specification at page 6, lines 25-28. Moreover, the specification provides examples of intended targets. Amendment filed March 24, 2003, at page 5 and Specification at page 7, line 14 through page 8, line 14. Lastly, the specification provides examples of the structure of the targeting element at, for example, page 8, line 21 through page 9, line 14. Applicants maintain that the claims must be read in view of the specification, and that "no claim may be read apart from and independent of the supporting disclosure on which it is based." See M.P.E.P. §§ 2173.02-2173.03; *see also In re Cohn*, 438 F.2d 989, 169 U.S.P.Q. 95 (C.C.P.A. 1971).

For the reasons above, Applicants respectfully request the reconsideration and withdrawal of the rejection of claims 34-38 under 35 U.S.C. § 112, second paragraph.

IV. Conclusion

In view of the foregoing remarks, Applicants submit that this claimed invention is not rendered obvious in view of the prior art references cited by the Examiner.

Moreover, the claims are definite. Applicants therefore request the reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Should the Examiner feel that this application is not in condition for allowance,

Applicants request that she contact the undersigned representative at 202-408-4185.

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If there is any fee due in connection with the filing of this Amendment, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

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